

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problems Mailbox.**

THIS PAGE BLANK (USPTO)

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61M 37/00, A61N 1/30	A1	(11) International Publication Number: WO 99/29364
		(43) International Publication Date: 17 June 1999 (17.06.99)

(21) International Application Number: PCT/US98/26158

(22) International Filing Date: 9 December 1998 (09.12.98)

(30) Priority Data:
60/069,340 11 December 1997 (11.12.97) US

(71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

(72) Inventor: ZUCK, Michael, G.; 22855 McGrath Road, Bend, OR 97701 (US).

(74) Agents: MILLER, D., Byron et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

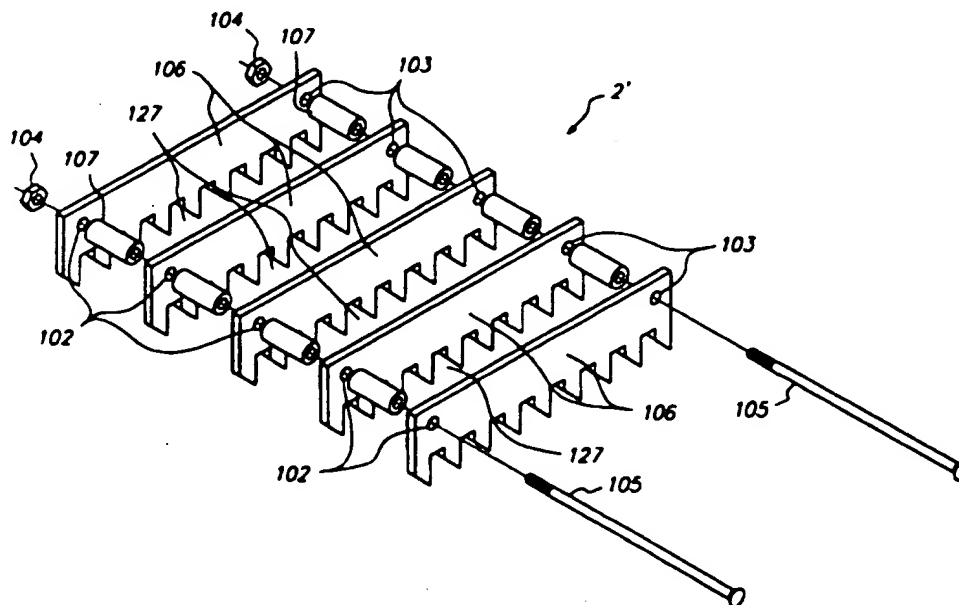
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DEVICE FOR ENHANCING TRANSDERMAL AGENT FLUX



(57) Abstract

A device (2) comprising a sheet member (6) having a plurality of microprotrusions (4) extending from a bottom edge (5) for penetrating the skin of a patient. The sheet member (6) when in use being oriented in an approximately perpendicular relation to the patient's skin.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

1 **DEVICE FOR ENHANCING**
2 **TRANSDERMAL AGENT FLUX**

3
4
5 **TECHNICAL FIELD**

6
7 The present invention relates to transdermal agent delivery and
8 sampling. More particularly, this invention relates to the transdermal delivery
9 of agents, such as peptides and proteins, through the skin, as well as the
10 transdermal sampling of agents from the body, such as glucose, other body
11 analytes and substances of abuse, such as alcohol and illicit drugs.

12
13 **BACKGROUND ART**

14
15 Interest in the percutaneous or transdermal delivery of peptides and
16 proteins to the human body continues to grow with the increasing number of
17 medically useful peptides and proteins becoming available in large quantities
18 and pure form. The transdermal delivery of peptides and proteins still faces
19 significant problems. In many instances, the rate of delivery or flux of
20 polypeptides through the skin is insufficient to produce a desired therapeutic
21 effect due to their large size/high molecular weight and the resulting inability
22 to pass through natural pathways (pores, hair follicles, etc.) through skin. In
23 addition, polypeptides and proteins are easily degradable during penetration
24 of the skin, prior to reaching target cells. Likewise, the passive flux of water
25 soluble small molecules such as salts is limited.

26 One method of increasing the transdermal delivery of agents relies on
27 the application of an electric current across the body surface or on
28 "electrotransport". "Electrotransport" refers generally to the passage of a
29 beneficial agent, e.g., a drug or drug precursor, through a body surface such
30 as skin, mucous membranes, nails, and the like. The transport of the agent is
31 induced or enhanced by the application of an electrical potential, which results
32 in the application of electric current, which delivers or enhances delivery of the
33 agent. The electrotransport of agents through a body surface may be attained

1 in various manners. One widely used electrotransport process, iontophoresis,
2 involves the electrically induced transport of charged ions. Electroosmosis,
3 another type of electrotransport process, involves the movement of a solvent
4 with the agent through a membrane under the influence of an electric field.
5 Electroporation, still another type of electrotransport, involves the passage of
6 an agent through pores formed by applying a high voltage electrical pulse to a
7 membrane. In many instances, more than one of these processes may be
8 occurring simultaneously to different extents. Accordingly, the term
9 "electrotransport" is given herein its broadest possible interpretation, to
10 include the electrically induced or enhanced transport of at least one charged
11 or uncharged agent, or mixtures thereof, regardless of the specific
12 mechanism(s) by which the agent is actually being transported.
13 Electrotransport delivery generally increases transdermal flux of agents,
14 particularly large molecular weight species (e.g., polypeptides), relative to
15 passive or non-electrically assisted transdermal delivery. However, further
16 increases in transdermal delivery rates and reductions in polypeptide
17 degradation during transdermal delivery are highly desirable.

18 One method of increasing the agent transdermal delivery rate involves
19 pre-treating the skin with, or co-delivering with the beneficial agent, a skin
20 permeation enhancer. The term "permeation enhancer" is broadly used
21 herein to describe a substance which, when applied to a body surface through
22 which the agent is delivered, enhances its flux therethrough. The mechanism
23 may involve a reduction of the electrical resistance of the body surface to the
24 passage of the agent therethrough, an increase in the permselectivity and/or
25 permeability of the body surface, the creation of hydrophilic pathways through
26 the body surface, and/or a reduction in the degradation of the agent (e.g.,
27 degradation by skin enzymes) during electrotransport.

28 There have been many attempts to mechanically disrupt the skin in
29 order to enhance transdermal flux, such as, U.S. Patent Nos. 3,814,097
30 issued to Ganderton et al., 5,279,544 issued to Gross et al., 5,250,023 issued
31 to Lee et al., and 3,964,482 issued to Gerstel et al., U.S. Patent No. Re.

1 25,637 issued to Kravitz et al. and published PCT applications WO 96/37155;
2 WO 97/48440; and WO 97/48441. These devices typically utilize tubular or
3 cylindrical structures generally, although the Gerstel U.S. Patent and the latter
4 two PCT publications do disclose the use of other shapes, to pierce the outer
5 layer of the skin. The piercing elements disclosed in these references
6 generally extend perpendicular from a thin flat member, such as a pad or
7 metal sheet, which is placed on the skin surface. The flexible nature of the
8 flat member and the tubular shape of the piercing elements result in a variety
9 of short-comings, such as manufacturing difficulties, flexing of the flat member
10 when pressure is applied to the top of the device, uneven or poor penetration
11 of the skin by the microblades or microtubes resulting in low transdermal
12 agent flux and, for electrotransport, increased irritation due to concentrating
13 the drug flux through fewer pathways.

14 A further shortcoming of the devices disclosed in WO 97/48440 and
15 WO 97/48441 concerns the degree of difficulty in their manufacture. First, the
16 thin flexible metallic sheets/plates must be subjected to a photoetching
17 process to form openings in the sheet/plate through which the agent being
18 transdermally delivered or sampled can pass. The photoetching is also used
19 to form the microblades. However, a second punching step is required to
20 bend the microblades to an angle roughly perpendicular to the plane of the
21 sheet. Because of the tiny size of the openings (about 0.4 x 0.5 mm) and
22 because of the large number of openings (about 50 to 300 openings/cm²),
23 accurate alignment of the micropunches with the microopenings is
24 problematic and time consuming.

25

26

27

DESCRIPTION OF THE INVENTION

28

29 The present invention provides a device suitable for increasing
30 transdermal agent flux. The device has microprotrusions which consistently
31 and reliably penetrate a body surface (e.g., skin) to enhance agent delivery or

1 sampling. The device of the present invention can be manufactured in high
2 volumes and at low-cost. The device of the present invention can penetrate
3 the stratum comeum of skin with a plurality of microprotrusions to form
4 pathways through which a substance such as a drug can be introduced (i.e.,
5 delivery) or a substance such as a body analyte can be withdrawn (i.e.,
6 sampling). A principal advantage of the present invention is that the device
7 ensures uniform penetration (i.e., generating the same size and depth
8 pathways) by the microprotrusions across the width of the device.
9 Furthermore, the present invention reproducibly provides uniformity in
10 penetration from patient to patient.

11 In one aspect, the invention comprises a rigid structure which
12 comprises a thin sheet which in use is oriented with its width perpendicular to
13 the patient's body surface. The sheet has a plurality of microprotrusions in the
14 same plane as the sheet and extending outward from a body proximal edge of
15 the sheet for piercing the body surface. The thin sheet transmits force applied
16 to a body distal edge of the sheet to the microprotrusions with substantially
17 less dissipation of the application force in the thin sheet than prior art devices.
18 The rigid structure formed by the thin sheet provides assured transmittance of
19 an externally applied load to the microprotrusions without wasting energy in
20 deflection of any portion of the device for easier, complete and reproducible
21 skin penetration. The improved penetration of the skin by the
22 microprotrusions because of the rigid structure formed by the thin sheet is
23 particularly beneficial in producing increased agent flux. The transmitted load
24 provides nearly complete penetration by all of the microprotrusions so as to
25 produce a substantial number of microslits in the stratum comeum for
26 continued and reproducible transdermal agent flux. Optionally, though
27 preferably, the rigid structure forms a void for containing an agent reservoir.
28 The void can be filled with a reservoir material for containing the agent to be
29 delivered or sampled.

30 The sheet with the plurality of microprotrusions can be manufactured
31 more easily and less expensively than the prior art designs comprised of a

1 thin sheet having blades punched perpendicularly therefrom since the present
2 invention does not require a separate punching operation.

3 In one aspect of the invention, the device utilizes a plurality of spaced
4 sheet members which are fastened together in a roughly parallel
5 configuration, each of the sheet members having a plurality of
6 microprotrusions extending downward from their body proximal edges.

7 In another aspect of the invention, the device utilizes a sheet member
8 folded in a serpentine configuration and having a plurality of microprotrusions
9 extending downward from the body proximal edge of the sheet member.

10 In another aspect of the invention, the device utilizes a plurality of
11 cylindrical sheet members forming concentric circles having a plurality of
12 microprotrusions extending downward from their body proximal edges,
13 respectively.

14 In yet another aspect of the invention, the device utilizes a sheet
15 member coiled in a loose spiral and having a plurality of microprotrusions
16 extending downward from the body proximal edge of the sheet member.

17 Optionally, though preferably, the device has a rigid support member
18 contacting the body distal edge(s) of the sheet member(s) opposite the body
19 proximal edge. The device of the present invention can be used in connection
20 with agent delivery, agent sampling or both. In particular the device of the
21 present invention is used in connection with transdermal drug delivery,
22 transdermal analyte sampling, or both. Delivery devices for use with the
23 present invention include, but are not limited to, electrotransport devices,
24 passive devices, osmotic devices and pressure driven devices. Sampling
25 devices for use with the present invention include, but are not limited to,
26 reverse electrotransport devices, passive devices, negative pressure driven,
27 and osmotic devices.

28

29

30

31

BRIEF DESCRIPTION OF THE DRAWINGS

In the figures, like reference numerals refer to like elements in the several drawings.

Figure 1 is a perspective view of a first embodiment of a skin penetrating sheet member and a rigid support therefor;

Figure 2 is a front elevational view of a portion of the sheet member of Figure 1 prior to being coiled;

Figure 3 is a perspective view of a second embodiment of a skin penetrating sheet member;

Figure 4 is a perspective view of a third embodiment of the skin penetrating sheet member;

Figure 5 is a cross-sectional view of the rigid support and skin penetrating sheet member of Figure 1 taken along line 5-5 with an agent-containing material within the voids between successive spirals of the sheet member;

Figure 6 is a front elevational view of a portion of a fourth embodiment of a sheet member prior to forming the sheet member into a pattern;

Figure 7 is a bottom perspective view of the sheet member of Figure 6 after being formed into a pattern;

Figure 8 is an alternate embodiment for microprotrusions on the sheet member;

1 Figure 9 is an exploded perspective view of one embodiment of an
2 electrotransport agent delivery/sampling system according to one
3 embodiment of the present invention;
4

5 Figure 10 is a bottom plan view of the electrotransport agent
6 delivery/sampling system of Figure 9;
7

8 Figure 11 is a right side elevational view of the electrotransport agent
9 delivery/sampling system of Figure 9;

10 Figure 12 is a rear elevational view of the electrotransport agent
11 delivery/sampling system of Figure 9;
12

13 Figure 13 is a cross-sectional view taken along line 13-13 of the
14 assembled electrotransport agent delivery/sampling system of Figure 11;
15

16 Figure 14 is a diagrammatic cross-sectional view of a passive agent
17 delivery/sampling system in accordance with one embodiment of the present
18 invention; and
19

20 Figure 15 is an exploded view of another embodiment of the skin
21 penetrating sheet member.
22

23 MODES FOR CARRYING OUT THE INVENTION

24

25 Turning now to the drawings in detail, the skin penetrating and
26 reservoir device 2 of the present invention is generally shown in Figure 1 for
27 use in the percutaneous administration or sampling of an agent. The terms
28 "substance", "agent" and "drug" are used interchangeably herein and broadly
29 include physiologically or pharmacologically active substances for producing a
30 localized or systemic effect or effects in mammals including humans and
31 primates, avians, valuable domestic household, sport or farm animals, or for

1 administering to laboratory animals such as mice, rats, guinea pigs, and the
2 like. These terms also include substances such as glucose, other body
3 analytes found in the tissue, interstitial fluid and/or blood, substances such as
4 alcohol, licit substances, illicit drugs, etc. that can be sampled through the
5 skin. The major barrier properties of the skin, such as resistance to agent
6 electrotransport of water soluble drugs, reside with the outer layer (i.e.,
7 stratum corneum). The inner portions of the epidermis generally comprise
8 three layers commonly identified as stratum granulosum, stratum malpighii,
9 and stratum germinativum. There is much lower resistance to transport or to
10 absorption of an agent through the stratum granulosum, stratum malpighii,
11 and stratum germinativum compared to the resistance to agent transport
12 through the stratum corneum. Thus, the microprotrusions 4 penetrate at least
13 through the stratum corneum so that the agent is conducted with little or no
14 resistance through the skin.

15 Device 2 comprises a plurality of microprotrusions 4 extending outward
16 from edge 5 (also referred to as the body proximal edge) of a thin, sheet
17 member or strip 6 (Figure 2). Sheet member 6 is generally compliant and
18 flexible because of its relatively thin thickness, for example, about 5 μm to
19 about 100 μm , preferably about 25 μm to about 50 μm . Coiling (Figure 1),
20 folding (Figures 4 and 7), curving (Figure 3), stacking (Figure 15), as well as
21 other forms of forming the sheet member 6 from its generally planer state
22 along its entire length, form a rigid structure having a plurality of voids 27, 127
23 for holding a reservoir that contains the agent that is to be delivered or that is
24 adapted to receive the agent that is to be sampled. Those skilled in the art
25 will appreciate that spacers can be placed within voids 27, optionally secured
26 together with fasteners such as fastening bolts or pins, to keep the spacing
27 between adjacent turns (Figure 1) or folds (Figure 4) of sheet member 6
28 constant. To prevent deformation or flexing side to side of sheet member 6 as
29 the microprotrusion array is applied to the body surface, support member 15
30 is preferably placed across the skin distal edge 7 (also referred to as the top
31 edge) of sheet member 6 (Figures 1 and 5).

1 Optional support member 15 can be a variety of configurations, for
2 example but not limited to the embodiments shown in Figures 1 and 5. The
3 support member 15 transmits force that is applied to the top of the support
4 member across the skin distal edge 7 of sheet member 6 so that each of the
5 microprotrusions 4 receive substantially the same amount of force for
6 penetrating the skin. Force applied to the edge 7, and directed toward the
7 skin, causes the microprotrusions 4 to pierce at least through the stratum
8 corneum.

9 Various embodiments of the device 2 are illustrated in the figures
10 although other configurations beyond those specifically illustrated are within
11 the scope of the invention. In each of these embodiments, the device 2 is
12 comprised of sheet member 6, or a plurality of sheet members 6, 106 (see
13 Figures 3 and 15) having their width oriented generally perpendicular to a
14 body surface (e.g., skin), thereby forming vertical walls, to efficiently (i.e.,
15 without bending or flexing the sheet member 6) transmit a force applied
16 across the skin distal edge 7 of the sheet member 6 to the microprotrusions 4.
17 The width (i.e., the distance from the skin distal edge to the skin proximal
18 edge) of the sheet member 6 is optionally, though preferably, sufficient to
19 create a plurality of voids 27 for the agent reservoir. The number and the
20 volume of voids 27 depends on a variety of factors, for example, the relative
21 structural integrity or flexibility of the sheet member 6, the distance across the
22 device 2, the size of the agent reservoir skin-contact area, and the reservoir
23 volume required for the therapy (in the case of drug delivery from the
24 reservoir).

25 A particularly preferred configuration for the device is illustrated in
26 Figure 15 and comprises a plurality of individual sheet members 106 stacked
27 together to form device 2'. Each of the sheet members 106 has a pair of
28 holes 102, 103, through which bolts 105 are inserted. Spacers (e.g., tubes)
29 107 are positioned between each adjacent pair of sheet members 106 to form
30 voids 127 therebetween. The spaced sheet members 106 are held together
31 as a unit by securing nuts 104 on the ends of bolts 105, or using other known

1 fasteners. As in the Figure 1 device, the voids 127 can be filled with a
2 reservoir matrix material (e.g., a gel) adapted to contain the beneficial agent
3 to be delivered or to receive the body analyte to be sampled. Those skilled in
4 the art will appreciate that spacers having other than tube-like configurations
5 (e.g., square or rectangular blocks) can also be used to provide voids 127
6 between adjacent sheet members 106 as long as the spacers do not form a
7 complete barrier between the agent reservoir 8 (i.e., the agent reservoir
8 contained in the voids 127) and the skin. Furthermore, more than two sets of
9 bolts 105, or other fastening pins, may be used to secure the sheet members
10 106 and spacers 105 together.

11 The microprotrusions 4 can be microblades or any of a variety of
12 configurations for piercing the skin or body surface. The microprotrusions 4
13 penetrate the stratum corneum of the epidermis when pressure is applied to
14 the top (body distal side) of the support member 15 to increase the
15 administration of, or sampling of, an agent through a body surface. The term
16 "body surface" as used herein refers generally to the skin, mucous
17 membranes, and nails of an animal or human, and to the outer surface of a
18 plant. The microprotrusions 4 penetrate the body surface to create good
19 agent conduction from the system into the body, or vice versa. In some
20 configurations, spaces 9 (see Figure 2) are formed between each of the
21 microprotrusions 4 to create a lower blade density and/or to provide "stops"
22 which prevent the device from penetrating the body surface beyond the length
23 of the microprotrusions 4. The agent can be administered or sampled at a
24 controlled rate of release from or collection in the voids 27 housing the agent-
25 containing or agent-receiving reservoir through an agent rate controlling
26 material such as a flux control membrane (not shown) positioned between the
27 voids 27, 127 and the body surface.

28 The microprotrusions or microblades 4 are generally formed from a
29 single piece of material (as shown in Figure 2) and are sufficiently sharp and
30 long for penetrating at least the stratum corneum of the skin. In one
31 embodiment, the microprotrusions 4 and the sheet member 6 are essentially

1 impermeable or are impermeable to the passage of an agent. The width of
2 each microprotrusion 4 can be any of a range of widths. The width of the
3 microprotrusion 4 at the intersection of the microprotrusion and the body
4 surface after the microprotrusion array has been inserted is typically at least
5 about 25 μm . The required length of the blades is subject to variation of the
6 body surface being penetrated and corresponds to at least the natural
7 thickness of the stratum corneum, for one of the principal features of the
8 invention is that the microprotrusions are to penetrate at least through the
9 stratum corneum and into the epidermis. Usually, the microprotrusions 4 will
10 have a length and configuration which achieves a depth of penetration of
11 about 25 μm to about 400 μm , with the depth of penetration for most
12 applications being between about 50 μm to about 200 μm . The
13 microprotrusions 4 can have slanted (i.e., angled) leading edges to further
14 reduce the insertion force required to press the microprotrusions into the skin
15 tissue. The leading edges of each microprotrusion 4 can all be the same
16 angle or can be at different angles suitable for penetrating the skin.
17 Alternatively, the leading edge of each microprotrusion 4 can be curved
18 having, for example, a convex or concave shape or be divided into any
19 number of angled segments such as the first segment being relatively steep
20 with respect to vertical and the second segment being more gradually angled
21 with respect to vertical.

22 The sheet member 6 of the present invention can optionally include
23 microprotrusion anchoring means for improving the attachment of the device
24 to the skin so that a continuous agent conducting pathway through the body
25 surface is preserved even during movement of the patient and/or the patient's
26 body surface. Some or all of the microprotrusions 4 can have a barb which
27 assists in anchoring the sheet member 6 and any corresponding device or
28 structure used in combination therewith to the skin. Microblade anchoring
29 barbs are described in more detail in WO 97/48440, and Reed et al. U.S.
30 Patents 5,312,456 and 5,569,272 of which any of the disclosed configurations
31 can be used with the present invention. The barbs are but one example of

1 microprotrusion anchoring means. In addition to anchoring means on the
2 blades, other means for holding the device in contact with the skin can be
3 used, such as but not limited to adhesive agent-containing reservoirs in the
4 voids 27, 127, peripheral adhesive, tape, a strap, or an elastic bandage.

5 The microprotrusion configurations of Figures 6, 7 and 8 facilitate
6 penetration of the body surface but also assist in anchoring the device to the
7 body surface. Sheet member 6 in Figure 6 has angled or slanted
8 microprotrusions 4. In sections 72 and 76 of sheet member 6, the
9 microprotrusions 4 are slanted to the right along the length of the sheet
10 member 6. In section 74, the microprotrusions are slanted to the left along
11 the length of the sheet member 6. As a result, when sheet member 6 is
12 folded along lines 78 into the serpentine pattern shown in Figure 7, all of the
13 microprotrusions 4 are slanted in the same direction. With this configuration,
14 the sheet member 6 and elements attached thereto can be slid along the body
15 surface in the direction of the slanted microprotrusions while pressing down
16 on the device to facilitate better penetration against the viscoelastic nature of
17 the body surface. This configuration also aids in anchoring the device to the
18 body surface because the top edges 80 of each of the microprotrusions act
19 similar to the barbs described previously.

20 Similarly, sheet member 6 in Figure 8 has curved, sweeping
21 microprotrusions 4. The microprotrusions 4 sweep to the left along the length
22 of the sheet member 6. As a result, when sheet member 6 is formed into a
23 curved configuration, such as for example those of either Figures 1 or 3, sheet
24 member 6 and elements attached thereto can be turned clockwise in the
25 direction of the sweeping microprotrusions while pressing down on the device
26 to facilitate better penetration against the viscoelastic nature of the body
27 surface. This configuration also aids in anchoring the device to the body
28 surface because the top edges 80 on each of the microprotrusions act similar
29 to the barbs described previously.

30 The pattern for the microprotrusion array members 6 can be produced
31 with a photolithography process followed by a chemical etching process. A

1 thin sheet member 6 of metal such as stainless steel or titanium is patterned
2 photo-lithographically with patterns containing blade-like structures. In
3 general, a thin laminate dry resist or wet resist is applied on the sheet
4 member 6 which typically has a thickness of about 7 μm to about 100 μm ,
5 preferably about 25 μm to about 50 μm . The resist is contact exposed using a
6 mask having the desired pattern and is subsequently developed. These
7 operations are conducted in much the same way that they are for the
8 manufacture of a printed circuit board. The sheet member 6 is then etched
9 using acidic solutions. After the pattern has been etched, the sheet member 6
10 is rolled or folded into the desired configuration (i.e., spiral, serpentine,
11 concentric circles, etc.) having voids 27 for holding the agent-containing
12 reservoir. The finished structure provides microprotrusions 4 at the skin
13 proximal edge 5 of sheet member 6. The adjacent turns of member 6 (see
14 Figures 1 and 5) form adjacent vertical walls between which are voids 27
15 containing a reservoir 8 (e.g., a gel reservoir; see Figure 5) for containing an
16 agent (e.g., a drug) therein or for the passage of an agent therethrough when
17 the sheet member 6 is applied to the body surface.

18 In one embodiment of the etching process, a dry resist (e.g.,
19 "DYNACHEM FL" (available from Dynachem located in Tustin, CA) is applied
20 12.5 μm thick to one or both sides of the sheet member 6 and exposed in a
21 standard manner. Then using a suitable spray etcher (e.g., "DYNAMIL VRP
22 10/NM" available from Western Tech. Assoc. located in Anaheim, CA) a
23 mixture of ferric chloride, water and hydrochloric acid is sprayed onto the
24 resist and sheet member 6 at about 52° C for two minutes. A standard
25 caustic stripper is used for the resist removal.

26 In another embodiment of the etching process, a wet resist (e.g.,
27 "SHIPLEY 111S" available from Shipley Corporation, located in Marlborough,
28 MA) is applied 7.5 μm thick at about 21° C to one or both sides of the sheet
29 member 6 and exposed in a standard manner. Then a suitable etchant (e.g.,
30 ferric chloride) is sprayed onto the resist and sheet member at about 49° C. A
31 standard caustic stripper is used for the resist removal.

1 The sheet member 6 and microprotrusions 4 are made from materials
2 that have sufficient strength and manufacturability to produce
3 microprotrusions, such as, glasses, ceramics, rigid polymers, reinforced (e.g.,
4 carbon fiber reinforced) polymers, metals and metal alloys. Examples of
5 metals and metal alloys include but are not limited to stainless steel, iron,
6 steel, tin, zinc, copper, gold, platinum, aluminum, germanium, zirconium,
7 titanium and titanium alloys. Each of the sheet member and microprotrusions
8 can have a thin layer of gold, platinum, iridium, titanium, or rhodium plating.
9 Examples of glasses include silicas and devitrified glasses such as
10 "PHOTOCERAM" available from Corning in Corning, NY. Examples of
11 polymers include but are not limited to polystyrene, polymethylmethacrylate,
12 polypropylene, polyethylene, "BAKELITE", cellulose acetate, ethylcellulose,
13 styrene/acrylonitrile copolymers, styrene/butadiene copolymers,
14 acrylonitrile/butadiene/styrene (ABS) copolymers, polyvinyl chloride and
15 acrylic acid polymers including polyacrylates and polymethacrylates.

16 The number of microprotrusions 4 and reservoirs 8 of any of the
17 embodiments of the sheet member 6 is variable with respect to the desired
18 flux rate, agent being sampled or delivered, delivery or sampling device used
19 (i.e., electrotransport, passive, osmotic, pressure driven, etc.), and other
20 factors as will be evident to one of ordinary skill in the art. In general, the
21 larger the number of microprotrusions per unit area (i.e., microblade density),
22 the less concentrated the flux of the agent in the skin because there are a
23 greater number of pathways through the skin. Consequently with
24 electrotransport delivery or sampling, a smaller number of microprotrusions
25 per unit area, leads to the transport of the agent through the skin becoming
26 more concentrated in fewer pathways. Higher concentrations of agents in a
27 skin pathway can lead to higher incidences and/or severity of skin reactions
28 (e.g., irritation). Therefore, larger microblade densities are generally preferred
29 to reduce the incidence and/or severity of skin reactions.

30 The present invention can also be used for sampling a body analyte
31 (e.g., glucose) transdermally. The analyte to be sampled is extracted through

1 the openings cut in the stratum comeum by the microprotrusions 4 and
2 collected in the sampling reservoir 8 (Figure 5). Known analyte (e.g., glucose)
3 sensing elements can be placed directly in reservoir 8. Alternatively, the
4 reservoir 8 can be removed from the device and suitably processed in order to
5 determine the amount of analyte collected. Such devices are useful in
6 monitoring the patient's blood glucose concentration (i.e., through appropriate
7 software which correlates the amount of glucose extracted with the
8 concentration of glucose in the blood) and can further be used to adjust a
9 treatment regime which typically includes administration of insulin to the
10 patient and/or appropriate modification of diet and/or exercise.

11 One embodiment of the present invention relies on the application of
12 an electric current across the body surface or "electrotransport". It will be
13 appreciated by those working in the field that the present invention can be
14 used in conjunction with a wide variety of electrotransport systems, as the
15 invention is not limited in any way in this regard. For examples of
16 electrotransport systems, reference may be had to U.S. Patent Nos.
17 5,147,296 to Theeuwes et al., 5,080,646 to Theeuwes et al., 5,169,382 to
18 Theeuwes et al., 5,423,739 to Phipps et al., 5,385,543 to Haak et al.,
19 5,310,404 to Gyory et al., and 5,169,383 to Gyory et al., of which any of the
20 disclosed electrotransport systems can be used with the present invention

21 Device 2 and support member 15 when used in an electrotransport
22 system are preferably electrically insulated from an electrode or other electric
23 current conducting members in order to avoid short circuiting the agent-
24 containing, or agent-receiving, reservoir contained in the voids 27, 127. This
25 can be accomplished by using electrically insulative materials or coatings for
26 sheet member 6, 106 and/or support member 15.

27 Figures 9-13 illustrate a representative electrotransport
28 delivery/sampling device 10 that may be used in conjunction with the present
29 invention. Device 10 comprises an upper housing 16, a circuit board
30 assembly 18, a lower housing 20, donor electrode 22, counter electrode 24,
31 donor reservoir in voids 27, counter reservoir 28 and skin-compatible

1 adhesive 30. Upper housing 16 has lateral wings 31 which assist in holding
2 device 10 on a patient's skin. Printed circuit board assembly 18 comprises an
3 integrated circuit 19 coupled to discrete components 40 and battery 32.
4 Circuit board assembly 18 is attached to housing 16 by posts (not shown in
5 the Figures) extending from the lower (skin proximal) surface of housing 16
6 and passing through openings 13a and 13b, the ends of the posts being
7 heated/melted in order to heat stake the circuit board assembly 18 to the
8 housing 16. Lower housing 20 is attached to the upper housing 16 by means
9 of adhesive layer 30, the upper surface 34 of adhesive layer 30 being adhered
10 to both lower housing 20 and upper housing 16 including the bottom surfaces
11 of wings 31. Shown (partially) on the underside of circuit board assembly 18
12 is a button cell battery 32. Other types of batteries may also be employed to
13 power device 10 depending on the need.

14 The device 10 is generally comprised of battery 32, electronic circuitry
15 19,40, electrodes 22,24, counter reservoir 28, and device 2 with sheet
16 member 6 and donor reservoir 8 therein, all of which are integrated into a self-
17 contained unit. Electrodes 22, 24, donor reservoir 8 and counter reservoir 28
18 are retained by lower housing 20. The outputs (not shown in Figure 18) of the
19 circuit board assembly 18 make electrical contact with the electrodes 24 and
20 22 through openings 23,23' in the depressions 25,25' formed in lower housing
21 20, by means of electrically conductive adhesive strips 42,42'. Electrodes 22
22 and 24, in turn, are in direct mechanical and electrical contact with the top
23 sides 44',44 of the donor reservoir 8 and counter reservoir 28. The bottom
24 side 46 of reservoir 28 contacts the patient's skin through the opening 29 in
25 adhesive layer 30. The bottom side 46' of the donor reservoir 8 contacts the
26 patient's skin through opening 29'. The agent (e.g., drug) in the donor
27 reservoir 8 is typically in the form of a solution, most preferably an aqueous
28 solution, which solution is contained in a solid matrix material such as a
29 sponge, a hydrophilic polymer matrix (e.g., a hydrogel) which allows free
30 mobility of the agent therethrough. The reservoir matrix material fills the voids

1 127 between adjacent sheet members 106 (as is more clearly shown in
2 Figure 15) such that the agent reservoir 8 is in contact with the body surface.

3 The device 10 adheres to the patient's body surface (e.g., skin) by
4 means of a peripheral adhesive layer 30 (which has upper adhesive side 34
5 and body-contacting adhesive side 36) and, optionally, anchoring elements on
6 the device 2 of any of the embodiments discussed herein. The adhesive side
7 36 covers the entire underneath side of the device 10 except where the
8 device 2 and the counter electrode reservoirs are located. The adhesive side
9 36 has adhesive properties which assures that the device 10 remains in place
10 on the body during normal user activity, and yet permits reasonable removal
11 after the predetermined (e.g., 24-hour) wear period. Upper adhesive side 34
12 adheres to lower housing 20 and retains the electrodes and agent reservoirs
13 within housing depression 25, 25' as well as retains device 2 to lower housing
14 20 and lower housing 20 to upper housing 16.

15 In one embodiment of the agent delivery/sampling device there is a
16 release liner (not shown) on the device 10 for maintaining the integrity of
17 adhesive layer 30 when the device is not in use. In use, the release liner is
18 stripped from the device before the device is applied to the skin. Device 10
19 also has a push button switch 12, which when pressed turns the device 10 on
20 which is made apparent to the user by means of LED 14 becoming lit. Agent
21 is delivered through the patient's skin (e.g., on the arm) by electrotransport
22 over the predetermined delivery interval.

23 In other embodiments of the present invention, passive transdermal
24 delivery or sampling devices are used with the device 2. It will be appreciated
25 by those working in the field that the present invention can be used in
26 conjunction with a wide variety of passive transdermal systems, as the
27 invention is not limited in this regard. For examples of passive systems,
28 reference may be had to, but not limited to, U.S. Patent Nos. 4,379,454 to
29 Campbell et al., 4,588,580 to Gale et al., 4,832,953 to Campbell et al.,
30 4,698,062 to Gale et al., 4,867,982 to Campbell et al., and 5,268,209 to Hunt
31 et al., of which any of the disclosed systems can be used with the present

1 invention. One example of a passive transdermal delivery/sampling device is
2 illustrated in Figure 14. Optional support member 15 having the body distal
3 edge of sheet member 6 embedded therein is housed in an outer housing 53
4 and a foam pad or band 57 which can be applied to the body surface. The
5 edges of sheet member 6 need not be embedded in the support member 15.
6 Support member 15 is sufficiently rigid so as not to deform when force is
7 applied thereto and so as to more evenly transmit the applied force to the top
8 edge of the sheet member 6 across the width and length of device 2.
9 Preferably, although not required, the passive delivery/sampling device has a
10 peripheral adhesive on the body-contacting surface of foam pad 57.

11 It will be appreciated by those working in the field that the present
12 invention can also be used in conjunction with a wide variety of osmotic and
13 pressure driven agent delivery or agent sampling systems, as the invention is
14 not limited to a particular device in this regard. For examples of osmotic and
15 pressure driven devices, reference may be had to U.S. Patent Nos. 4,340,480
16 to Eckenhoff, 4,655,766 to Theeuwes et al., 4,753,651 to Eckenhoff,
17 5,279,544 to Gross et al., 4,655,766 to Theeuwes, 5,242,406 to Gross et al.,
18 and 4,753,651 to Eckenhoff any of which can be used with the present
19 invention.

20 This invention has utility in connection with the delivery of agents within
21 any of the broad class of drugs normally delivered through body surfaces and
22 membranes, including skin. In general, this includes drugs in all of the major
23 therapeutic areas. The invention is also useful in the transdermal delivery of
24 proteins, peptides and fragments thereof, whether naturally occurring,
25 chemically synthesized or recombinantly produced. The invention may
26 additionally be used in conjunction with the delivery of vaccines, nucleotidic
27 drugs, including oligonucleotide drugs, polynucleotide drugs, and genes.
28 These substances typically have a molecular weight of at least about 300
29 daltons, and more typically have a molecular weight of at least about 300 to
30 40,000 daltons. As mentioned, the device 2 of the present invention can also
31 be used with sampling devices including, but not limited to, reverse

1 electrotransport (i.e., reverse iontophoresis and/or reverse electroosmosis in
2 the case of sampling uncharged materials such as glucose), osmosis, and
3 passive diffusion. For example, reference may be had to U.S. Patent Nos.
4 4,756,314 to Eckenhoff et al., 5,438,984 to Schoendorfer, 5,279,543 to
5 Glikfeld et al., and 5,362,307 to Guy et al.

6 It will be appreciated by those of ordinary skill in the art that the
7 invention can be embodied in other specific forms without departing from the
8 spirit or essential character thereof. The presently disclosed embodiments
9 are therefore considered in all respects to be illustrative and not restrictive.
10 The scope of the invention is indicated by the appended claims rather than
11 the foregoing description, and all changes which come within the meaning
12 and range of equivalents thereof are intended to be embraced therein.

1 CLAIMS:

2

3 1. A device (2) for use in introducing or withdrawing an agent through a body
4 surface, comprising a sheet member (6) having a plurality of microprotrusions
5 (4) for piercing the body surface, the device (2) being characterized by:

6 the plurality of microprotrusions (4) extending from an edge (5) of the
7 sheet member (6), the sheet member (6) when in use being oriented in an
8 approximately perpendicular relation to the body surface with the edge (5)
9 having the microprotrusions (4) being proximal the body surface.

10

11 2 The device of Claim 1, wherein the sheet member (6) has a
12 configuration which defines a void (27), and the device further comprises an
13 agent-containing or agent-receiving reservoir (8) in the void (27), the reservoir
14 (8) when in use being in agent transmitting communication with the body
15 surface.

16

17 3. The device of Claim 2, wherein a plurality of said sheet members (106)
18 are fastened together.

19

20 4 The device of Claim 3, wherein said sheet members (106) are fastened
21 together in spaced and roughly parallel orientation.

22

23 5. The device of Claim 2, wherein the sheet member (6) has a spiral
24 configuration and the void (27) is defined by adjacent spirals.

25

26 6 The device of Claim 2, wherein the sheet member (6) has a serpentine
27 configuration and the void (27) is defined by adjacent folds.

28

29 7. The device of Claim 2, wherein the sheet member (6) comprises a
30 plurality of concentric circular sheets (6) and the void (27) is defined by
31 adjacent concentric circular sheets (6).

1

2 8. The device of Claim 2, wherein the reservoir (8) is an agent-containing
3 reservoir.

4

5 9. The device of Claim 8, wherein the agent is a therapeutic agent.

6

7 10. The device of Claim 9, wherein the agent is a therapeutic drug.

8

9 11. The device of Claim 8, further comprising a therapeutic agent delivery
10 device (10).

11

12 12. The device of Claim 11, wherein the delivery device (10) comprises a
13 transdermal drug delivery device.

14

15 13. The device of Claim 2, wherein the reservoir (8) is an agent-receiving
16 reservoir.

17

18 14. The device of Claim 13, wherein the agent is a body analyte

19

20 15. The device of Claim 14, wherein the body analyte is glucose.

21

22 16. The device of Claim 13, further comprising an agent sampling device (10).

23

24 17. The device of Claim 16, wherein the sampling device (10) samples
25 glucose and measures or estimates concentration of glucose in the body.

26

27 18. The device of Claim 1, wherein the microprotrusions are in a plane
28 defined by the sheet member (6).

29

30 19. The device of Claim 2, further comprising a rigid structural support (15)
31 extending across at least a portion of the sheet member (6) configuration.

- 1
2 20. The device of Claim 19, wherein the rigid structural support (15)
3 contacts a second edge (7) of the sheet member (6) which second edge (7) is
4 opposite the edge (5) having the microprotrusions (4).
5

1/7

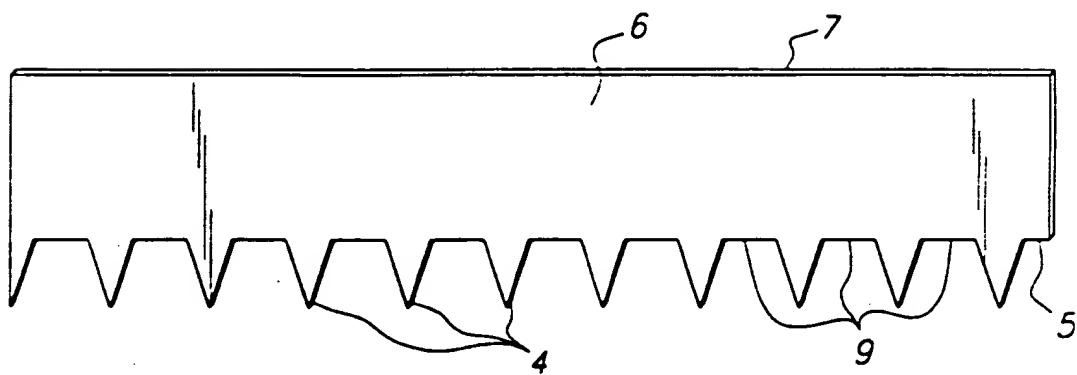
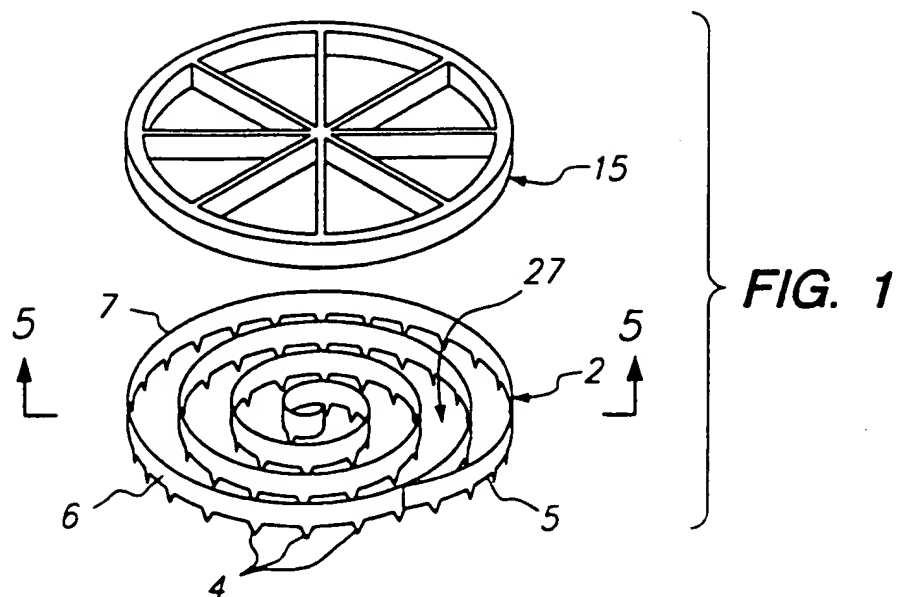


FIG. 2

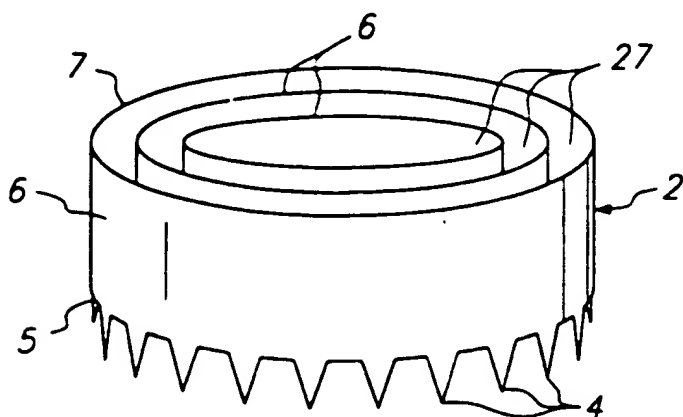


FIG. 3

2/7

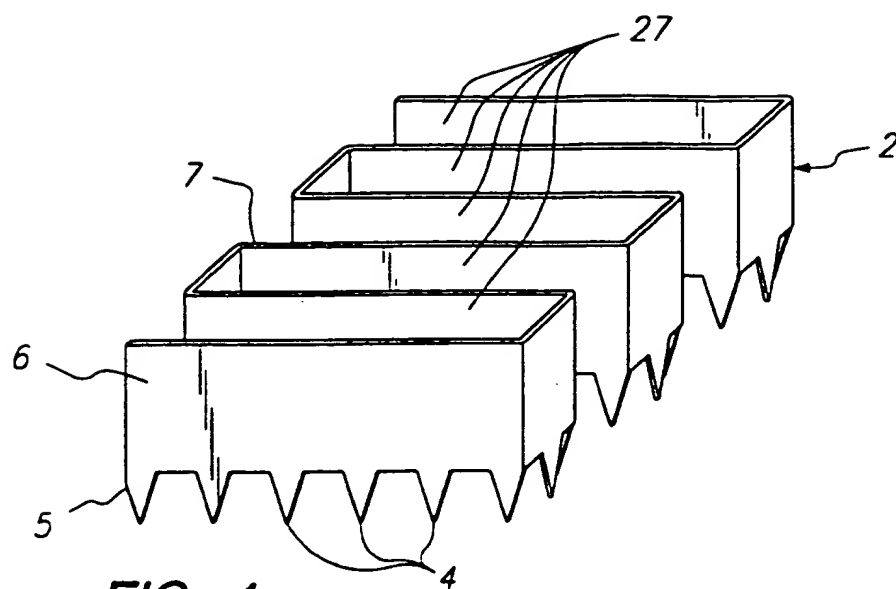


FIG. 4

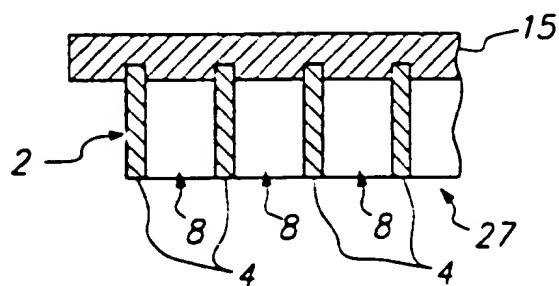


FIG. 5

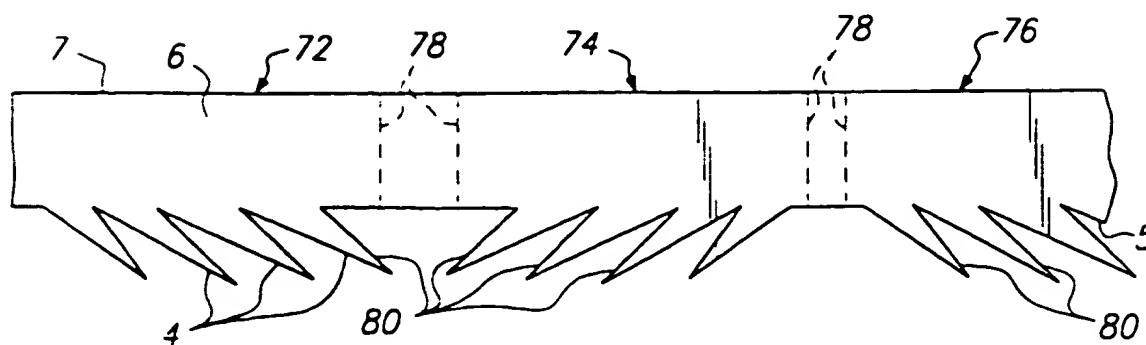


FIG. 6

3/7

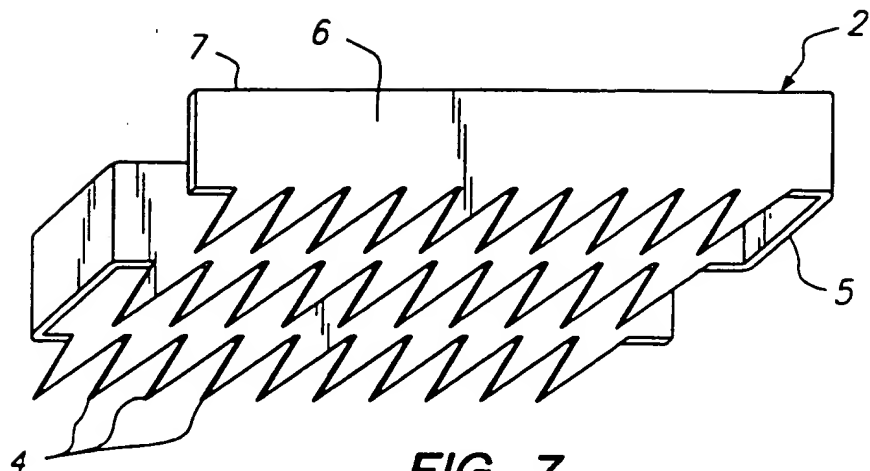


FIG. 7

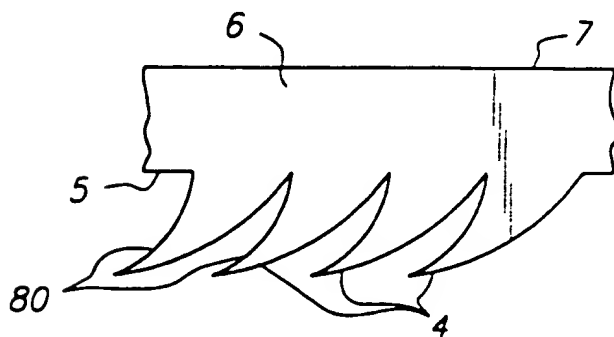
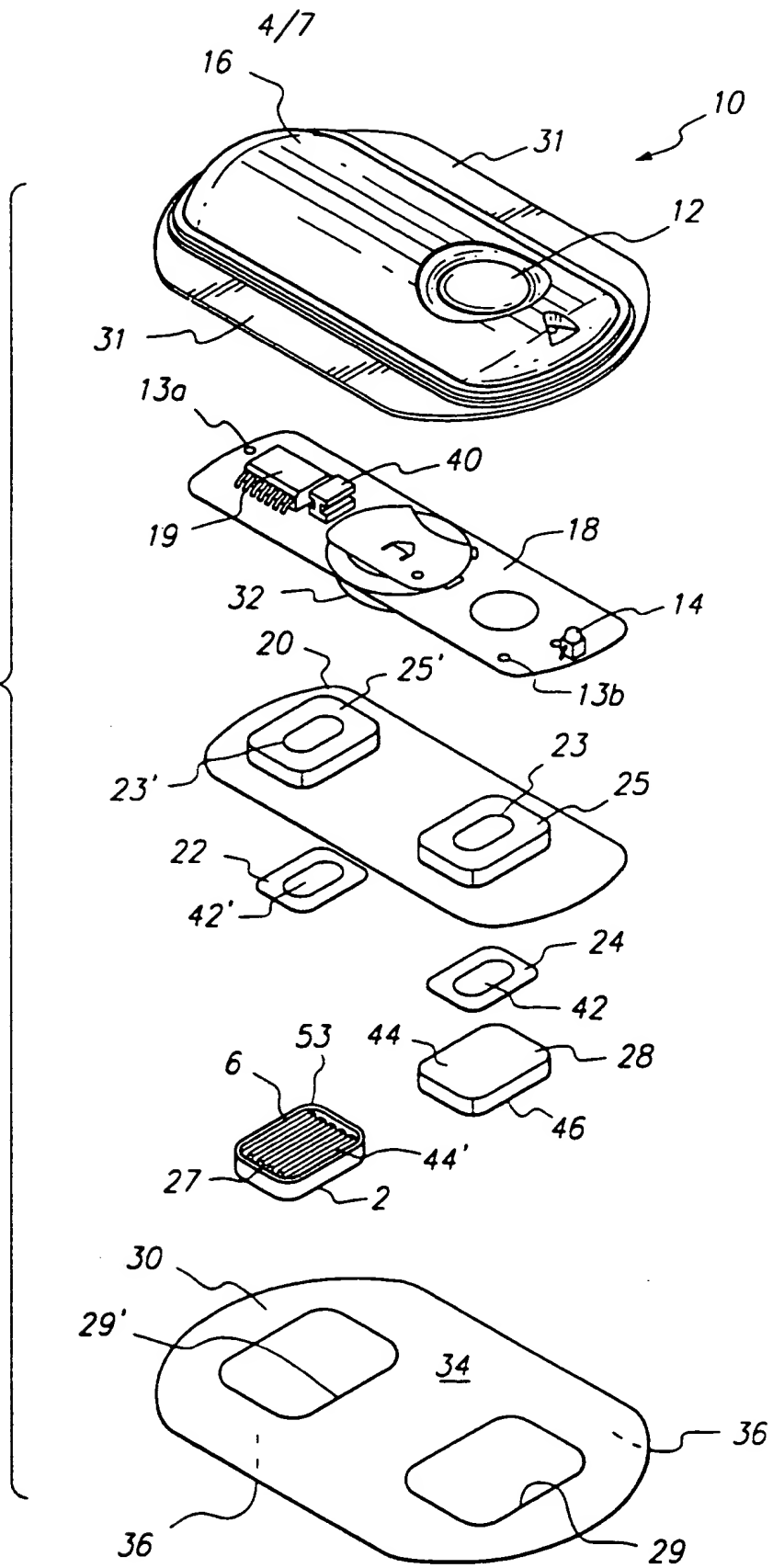
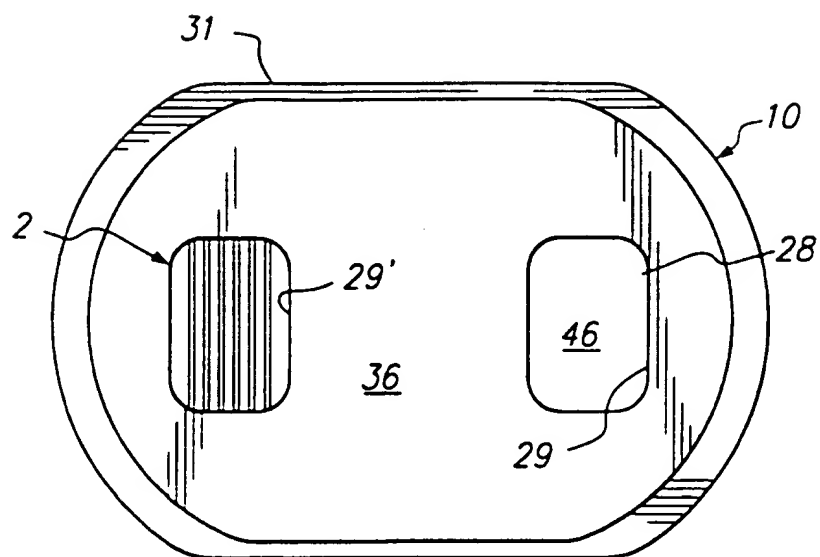
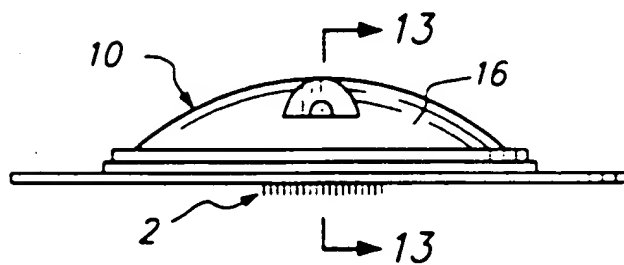


FIG. 8

FIG. 9



5/7

**FIG. 10****FIG. 11**

6/7

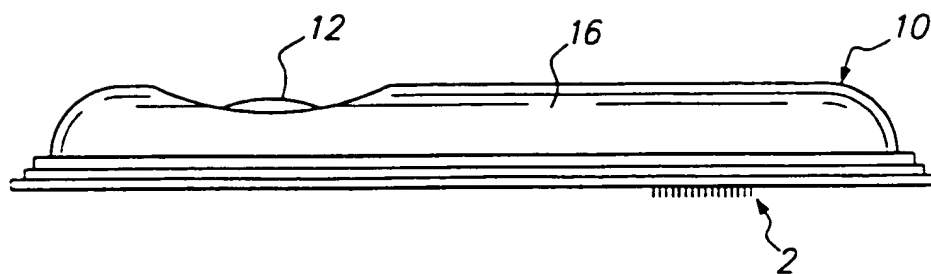


FIG. 12

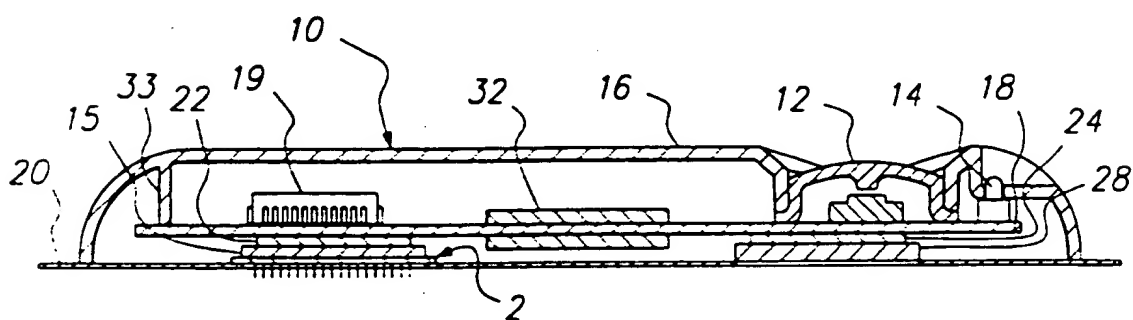


FIG. 13

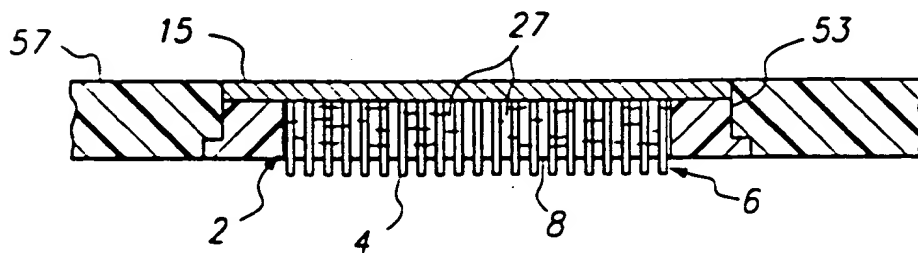


FIG. 14

7/7

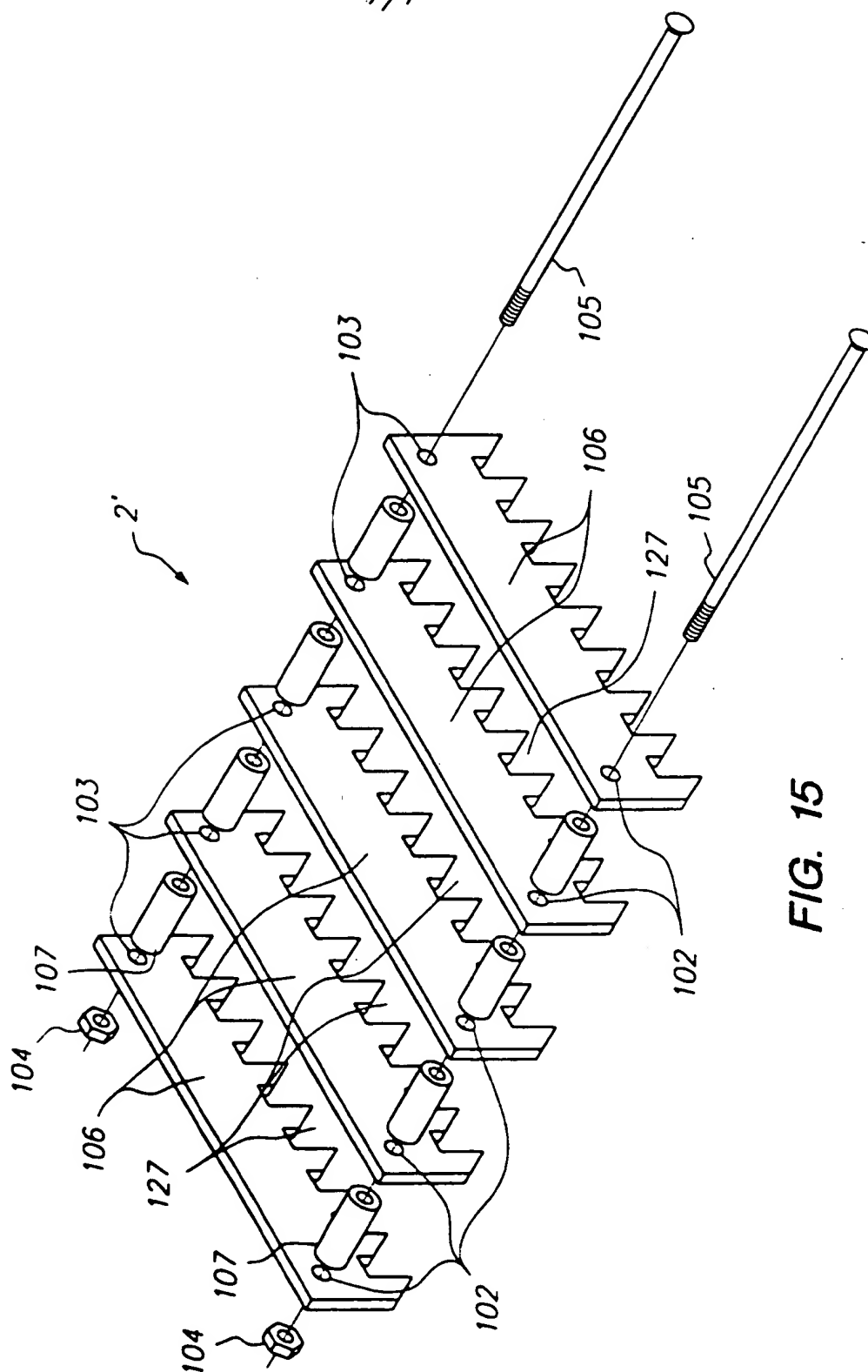


FIG. 15

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/26158

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M37/00 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M A61N A61K A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 5 611 806 A (JANG) 18 March 1997 see column 3, line 41 - column 5, line 17; figures ---	1
X	DE 195 18 974 A (SAMSUNG) 30 November 1995 see column 8, line 10 - column 12, line 30; figures ---	1
A	US 3 072 122 A (ROSENTHAL) 8 January 1963 see claim 1; figures ---	1,2
A	EP 0 497 620 A (CARNEGIE-MELLON) 5 August 1992 cited in the application see column 5, line 43 - column 6, line 39; figure 13 --- -/-	1,2, 8-11,13

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

*** Special categories of cited documents**

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- * "S" document member of the same patent family

Date of the actual completion of the international search

3 May 1999

Date of making of the international search report

11/05/1999

Name and mailing address of the ISA

European Patent Office P B 5816 Patentlaan 2
NL 2280 HV Rijswijk
Tel (+31-70) 340-2040, Te 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer

Kousouretas, I

INTERNATIONAL SEARCH REPORT

In tional Application No

PCT/US 98/26158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 17648 A (CIBA-GEIGY) 13 June 1996 see abstract; figures -----	1,8-13
A	US 3 964 482 A (GERSTEL) 22 June 1976 see abstract; figures -----	1,8-13
A	WO 96 37256 A (SILICON MICRODEVICES) 28 November 1996 cited in the application see abstract; figures -----	1,2,8-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/26158

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5611806	A	18-03-1997	KR 115807 Y	17-04-1998
			KR 115808 Y	17-04-1998
			CA 2149943 A	24-11-1995
			DE 19518932 A	30-11-1995
DE 19518974	A	30-11-1995	KR 115809 Y	17-04-1998
			KR 134154 B	14-04-1998
			KR 134153 B	14-04-1998
			KR 134150 B	14-04-1998
			CA 2149836 A	24-11-1995
			FR 2720002 A	24-11-1995
			JP 2605237 B	30-04-1997
			JP 8150146 A	11-06-1996
US 3072122	A	08-01-1963	FR 1245282 A	01-02-1961
			GB 878788 A	
EP 497620	A	05-08-1992	US 5312456 A	17-05-1994
			AT 169090 T	15-08-1998
			DE 69226384 D	03-09-1998
			DE 69226384 T	17-12-1998
			JP 6323310 A	25-11-1994
			US 5569272 A	29-10-1996
			US 5676850 A	14-10-1997
WO 9617648	A	13-06-1996	AT 177325 T	15-03-1999
			AU 4256496 A	26-06-1996
			CA 2205444 A	13-06-1996
			DE 59505328 D	15-04-1999
			EP 0796128 A	24-09-1997
			JP 10510175 T	06-10-1998
US 3964482	A	22-06-1976	NONE	
WO 9637256	A	28-11-1996	AU 5869796 A	11-12-1996